Patent claims

1. Neurotrypsins of the formulas I and II

I: neurotrypsin of the human

II: neurotrypsin of the mouse

comprising the separate, coding and coded sequences of these compounds of the formulas I or II, comprising the separate partial sequences of the coding and coded sequences of these compounds of the formulas I or II, as for example the coding and coded sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding or coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding or coded sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding or coded sequences, or parts thereof, of the compounds of the formulas I or II, whose biological activity is equal or similar to that of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the translation products of the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or to parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but, as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

2. Pharmaceutical composition, characterized in that it contains as at least one active compound either the coded sequence or the coding sequence of the compound of the formula I or of the formula II, or the separate partial sequences of the coded and coding sequences of these compounds of the formulas I or II, as for example the coding or coded sequences of the catalytic domains, comprising the coding or coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding or coded sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising all

sequence variants of the coding or coded sequences, or parts thereof, of the compounds of formulas I or II, whose biological activity is equal or similar to that of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the translation products of the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or to parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of formulas I or II, or parts thereof, but, as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

3. Pharmaceutical composition, characterized in that it contains as at least one active compound a substance which changes the function of the coded sequence of the compounds of formulas I or II, for example, in that it reduces or increases the catalytic activity of the coded protein, or a part thereof, or in that it shortens or prolongs the time of presence of the coded protein at its place of action in the body.

4. Pharmaceutical composition, characterized in that it contains as at least one active compound a substance which changes the expression of the coding or coded sequences of the compounds of formulas I or II, for example in that it enhances or inhibits the transcription of the mRNA or in that it enhances or inhibits the translation of the coded sequences of the compounds of formulas I or II.

5. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents or reduces the growth, the expansion, the infiltration and the metastasis of primary and metastatic tumors, as for example brain tumors or tumors of the retina.

6. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it contributes to the minimization of the tissue destruction in stroke, including brain infarction and ischemia, intracerebral hemorrhage, and subarrachnoid hemorrhage, as for example by exerting a protecting effect on the cells of the so-called penumbra zone surrounding the necrotic tissue.

7. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it contributes to the minimization of the tissue destruction in traumatic brain injury, as for example by exerting a protective effect on the cells of the so-called zone surrounding the necrotic tissue.

8. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents, ameliorates or cures the negative effects caused by neurodegenerative diseases.

9. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents, ameliorates or cures the negative effects caused by neuroinflammatory diseases, as for example multiple sclerosis.

10. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it reduces or prevents negative effects on brain tissue caused by epileptic seizures.

11. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it contributes to the rescue of endangered neurons, as for example neurons endangered by hypoxia and ischemia, axotomy, nerve transection, deafferentiation, excitotoxicity, neuroinflammatory diseases and processes, epileptic seizures, and cancerous neoformations.

12. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it contributes to axonal regeneration and/or restoration of synaptic integrity and functions.

13. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents, ameliorates, or cures retinal disorders, as for example retinal degeneration and retinal neoangiogenesis.

14. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents cell death, comprising apoptosis and other forms of cell death, in the nervous system.

15. Pharmaceutical composition according to claim 14, characterized in that the cell death is an cell death in connection with damages of the nervous tissue, for example infarct of the brain and ischemic stroke, or hemorrhage of the brain, or trauma of the brain.

16. Pharmaceutical composition according to claim 14, characterized in that the cell deathis an cell death in connection with damages of the nervous tissue, which occur due to lack of oxygen or glucose or due to intoxication.

17. Pharmaceutical composition according to claim 14, characterized in that the cell death is an cell death in connection with epileptic seizures.

18. Pharmaceutical composition according to claim 14, characterized in that the cell death is an cell death in connection with neurodegenerative diseases and inherited genetic deficiencies of the nervous system.

19. Pharmaceutical composition according to claim 14, characterized in that the cell death is an cell death in connection with axotomy or nerve transection, or deafferentiation.

20. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it influences the regeneration of injured, damaged, underdeveloped, or maldeveloped brain tissue and/or nervous tissue.

21. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it enhances the reorganization of the brain or nervous areas that have remained intact after brain and/or nerve injuries or after the destruction or damage of brain areas.

22. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it prevents, ameliorates, or cures pathological pain syndromes.

23. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it contributes to the improvement of the brain performance in healthy persons, as well as in persons with reduced brain performance.

24. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates the learning and memory functions in healthy persons, as well as in persons with reduced learning and memory functions.

25. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates or cures disorders in the field of disorders of the psychic wellness, or the psychosomatic state of health, as for example nervosity or „inner unrest".

26. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates or cures disorders in the field of the emotional functions, as for example states of anxiety.

27. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates or cures psychiatric disorders.

28. Pharmaceutical composition according to claim 27, characterized in that the psychiatric disorder is a disorder in the field of schizophrenia and schizophrenia-like disorders, comprising chronic schizophrenia, chronic schizo-affective disorders, unspecific disorders, comprising acute and chronic schizophrenia of various symptomatologies, as for example severe, non-remitting „Kraepelinic" schizophrenia, or as for example the DSM-III-R-prototype of the schizophrenia-like disorders, comprising episodic schizophrenic disorders, comprising delusionic schizophrenia-like disorders, comprising schizophrenia-like personality disorders, as for example schizophrenia-like personality disorders with mild symptomatics, comprising schizotypic personality disorders, comprising the latent forms of schizophrenic or schizophrenia-like disorders, comprising non-organic psychotic disorders.

29. Pharmaceutical composition according to claim 27, characterized in that the psychiatric disorder is a disorder in the field of the endogenic depressions or in the field of manic or manic-depressive disorders.

30. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates or cures disorders of the brain function due deficiency, malfunction, or overfunction of at least one protease.

31. Pharmaceutical composition according to claim 30, characterized in that the protease is tissue-type plasminogen activator, abbreviated as tPA, urokinase-type plasminogen activator, abbreviated as uPA, or plasmin.

32. Pharmaceutical composition according to claim 2, 3, or 4, characterized in that it ameliorates or cures disorders of the function of the lungs due to deficiency, malfunction, or overfunction of at least one protease.

33. Pharmaceutical composition according to claim 32, characterized in that the disorder of the function of the lungs is chronic bronchitis or emphysema of the lungs.

34. Use for the production of recombinant proteins of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of the compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding nucleotide sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences or partial sequences thereof of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of formulas I or II, whose translation products have a biological activity equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the formulas I or II, comprising the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but, as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

35. Use as targets for the development of pharmaceutical drugs, for example for the inhibition or the enhancement of the catalytic activity of the coded proteins of the formulas I or II, of proteins with the coded amino acid sequences of the compounds of the formulas I or II, comprising the proteins with the separate partial sequences of the coded amino acid sequences of the compounds of the formulas I or II, as for example

the separate catalytic domains of the compounds of the formulas I or II, comprising the proteins with the coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the proteins with the coded amino acid sequences or partial sequences thereof of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coded sequences, or parts thereof, of the compounds of formulas I or II, whose biological activity is equal or similar to the coded sequences of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the formulas I or II, comprising the proteins with the coded amino acid sequences, or partial sequences thereof, of the nucleotide sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions.

36. Use as targets for the development of pharmaceutical drugs, for example for the enhancement or the inhibition of the catalytic activity of the coded proteins of the formulas I or II, of the species-homologous proteins, or parts thereof, of the compounds of the formulas I or II, as for example the species-homologous proteins of the rat, the rabbit, the cow, the sheep, the pig, the primates, the birds, the zebra fish, the fruit fly (Drosophila melanogaster), etc., comprising the partial sequences thereof, as for example the separate catalytic domains, comprising the splice variants of the species-homologous proteins, comprising the alleles of the species-homologous proteins, comprising the translation products of the sequences hybridizing under stringent conditions to the corresponding species-homologous compounds of the formulas I or II, or their splice variants, or their alleles, of the coding sequences or partial sequences of the compounds of formulas I or II .

37. Use for the spatial structure determination, for example the spatial structure determination by means of crystallography or nuclear resonance spectroscopy, of the proteins with the coded amino acid sequences of the compounds of the formulas I or II, comprising the proteins with the separate partial sequences of the coded amino acid sequences of the compounds of the formulas I or II, as for example the separate catalytic domains, comprising the proteins with the coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the proteins with the coded amino acid sequences, or partial sequences thereof, of the corresponding alleles of the compounds of the formulas I or II, comprising

all sequence variants of the coded sequences, or parts thereof, of the compounds of the formulas I or II, whose biological activity is equal or similar to that of the coded sequences of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the formulas I or II, comprising the translation products with the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions, comprising the species-homologous proteins of the compounds of the formulas I or II, for example the species-homologous proteins of the rat, the rabbit, the cow, the sheep, the pig, the primates, the birds, the zebra fish, the fruit fly (Drosophila melanogaster), etc., comprising the partial sequences thereof, as for example the separate catalytic domains.

38. Use for the prediction of the protein structure by means of computerized protein structure prediction methods, of the coded amino acid sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coded amino acid sequences of the compounds of the formulas I or II, as for example the coded amino acid sequences of the separate catalytic domains of the compounds of the formulas I or II, comprising the coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coded amino acid sequences, or parts thereof, of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coded sequences, or parts thereof, of the compounds of the formulas I or II, whose biological activity is equal or similar to that of the coded sequences of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the formulas I or II, comprising the amino acid sequences of the translation products of the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions, comprising sequences of the species-homologous compounds of the compounds of the formulas I or II, for example the sequences of the species-homologous compounds of the rat, the rabbit, the cow, the sheep, the pig, the primates, the birds, the zebra fish, the fruit fly (Drosophila melanogaster), etc., comprising the partial sequences of the species-homologous compounds, as for example the sequences of the catalytic domains of the species-homologous compounds.

39. Use as targets for the development of pharmaceutical drugs , for example for the inhibition or the enhancement of the catalytic activity of the coded proteins of the compounds of the formulas I or II, of the spatial structure of the coded amino acid sequences of the compounds of the formulas I or II, comprising the spatial structures of the separate partial sequences of the compounds of the formulas I or II, as for example the spatial structure of the catalytic domains, comprising the spatial structure of the coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the spatial structure of the coded sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising the spatial structure of all sequence variants of the coded sequences, or parts thereof, of the compounds of formulas I or II, whose biological activity is equal or similar to the coded sequences of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the formulas I or II, comprising the spatial structures of the translation products of the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions, comprising the spatial structures of the species-homologous compounds of the compounds of the formulas I or II, as for example the spatial structures of the species homologous compounds, or parts thereof, of the rat, the rabbit, the cow, the sheep, the pig, the primates, the birds, the zebra fish, the fruit fly (Drosophila melanogaster), etc..

40. Use in gene therapeutical applications in humans and in animals, as for example as parts of gene therapy vectors or as for example as parts of artificial chromosomes, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino

acid sequence positions of the sequences of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

41. Use for so-called cell engineering applications for the production of gene technologically mutated cells, which produce the coded sequences, or parts thereof, of the compounds of the formulas I or II, for example for cell-therapeutical applications as a pharmaceutical composition according to claim 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, or 33, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

42. Use as antigens for the production of antibodies, as for example antibodies that inhibit or promote the protease function or antibodies that can be used for immunohistochemical studies, of the coded amino acid sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coded amino acid sequences of the compounds of the formulas I or II, as for example the coded amino

acid sequence of the catalytic domain or one or more of the other domains or segments, comprising the coded sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coded sequences or partial sequences of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coded sequences, or parts thereof, of the compounds of the formulas I or II, whose biological activity is equal or similar to that of the coded sequences of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the compounds of the formulas I or II, comprising the translation products or parts thereof, of the sequences hybridizing to the coding sequences of the compounds of the formulas I or II, or parts thereof, under stringent conditions, comprising the coded sequences of the species-homologous compounds of the compounds of the formulas I or II, as for example the coded sequences of the species-homologous compounds of the rat, the rabbit, the cow, the sheep, the pig, the primates, the birds, the zebra fish, the fruit fly (Drosophila melanogaster), etc., comprising the separate partial sequences of the coded sequences of the species-homologous compounds of the compounds of the formulas I or II, as for example the coded amino acid sequence of the catalytic domain, or one or more of the other domains or segments.

43. Use for the production of transgenic animals, as for example transgenic mice, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences, or partial sequences, of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the

compounds of the formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

44. Use for the inactivation or the mutation of the corresponding gene by means of gene targeting techniques, as for example the elimination of the gene in the mouse through homologous recombination, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences, or partial sequences, of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences, or partial sequences, of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequence of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

45. Use for the diagnostics of disorders in the gene corresponding to the compound of the formula I, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences, or partial sequences, of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example

sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.

46. Use as a starting sequence for gene technological modifications aimed at the production of pharmaceutical compositions or gene therapy vectors which exhibit changed properties as compared with the corresponding pharmaceutical compositions or gene therapy vectors containing the coding nucleotide sequence of the compounds of formulas I or II, for example changed proteolytic activity, changed proteolytic specificity, or changed pharmacokinetic characteristics, of the coding nucleotide sequences of the compounds of the formulas I or II, comprising the separate partial sequences of the coding sequences of these compounds of the formulas I or II, as for example the coding sequences of the catalytic domains of the compounds of the formulas I or II, comprising the coding sequences or partial sequences of the corresponding splice variants of the compounds of the formulas I or II, comprising the coding sequences, or partial sequences, of the corresponding alleles of the compounds of the formulas I or II, comprising all sequence variants of the coding sequences, or parts thereof, of the compounds of the formulas I or II, whose translation products exhibit a biological activity which is equal or similar to that of the translation products of the compounds of the formulas I or II, for example sequence variants of the compounds of the formulas I or II, which differ in the not conserved amino acid sequence positions of the sequences of the compounds of the formulas I or II, comprising the sequences hybridizing to the coding sequences, or parts thereof, under stringent conditions, comprising the nucleotide sequences coding the proteins coded by the compounds of the formulas I or II, or parts thereof, but as a result of the use of different alternative codons, are degenerated with regard to the nucleotide sequences defined by the compounds of the formulas I or II.